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1626

April 18, 2003

Commissioner for Patents
Washington, D.C. 20231

Re: U. S. Patent Appl. No. 09/994,927
Filed: November 28, 2001
For: **Bisubstituted Carbocyclic Cyclophilin Binding Compounds and Their Use**
Inventors: HAMILTON *et al.*
Our Ref: 03166.0029.NPUS02

Sir:

The following documents are forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Information Disclosure Statement;

2. Form PTO-1449 (4 pages) with 81 attached references;

3. Check no. 390567 in the amount of $180.00; and

4. Return postcard.

It is respectfully requested that the attached postcard be stamped with the filing date of these documents and returned to our courier.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No.08-3038 referencing docket number 03166.0029.NPUS02. If extensions of time under 37 C.F.R. § 1.136 other than those otherwise provided for herewith are required to prevent abandonment of the present patent application, then such extensions of time are hereby petitioned. A duplicate copy of this letter is enclosed.

Respectfully submitted,

Michael J. Bell (Reg.No. 39,604)
Michael J. Stimson (Reg. No. 45,429)

Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
HAMILTON, Gregory S., *et al.*

Appl. No. 09/994,927

Filed: November 28, 2001

For: **Bisubstituted Carbocyclic Cyclophilin Binding Compounds and Their Use**

Art Unit: 1626

Examiner: Gerstl

Attorney Docket: 03166.0029.NPUS020

Information Disclosure Statement

Commissioner for Patents
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted

herewith. It is further understood that the Examiner will consider information that had been cited by or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

Applicants have checked the appropriate boxes below.

☐ 1. This Information Disclosure Statement is being filed within three months of the U.S. filing date OR before the mailing date of a first Office Action on the merits. No statement under 37 C.F.R. § 1.97(e) or fee is required, or

☑ 2. This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection or Notice of Allowance, or action that otherwise closes prosecution in the application, and

☐ a. I hereby state that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1), or

☐ b. I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2), or

☑ c. Attached is our Check No. 390567 in the amount of $180.00 in payment of the fee under 37 C.F.R. § 1.17(p).

☐ 3. This Information Disclosure Statement is being filed more than three months after the U.S. filing date and after the mailing date of a Final Rejection or Notice of Allowance, but on or before payment of the Issue Fee. Attached is our Check No.

_____ in the amount of $ _____ in payment of the fee under 37 C.F.R. § 1.17(i), and

☐ a. I hereby state that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1), or

☐ b. I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 4. Relevance of the non-English language document(s) is discussed in the present specification.

☐ 5. The document(s) was/were cited in a corresponding foreign application. An English language version of the foreign search report is attached for the Examiner's information.

☐ 6. A concise explanation of the relevance of the non-English language document(s) appears below:

☐ 7. The Examiner's attention is directed to co-pending U.S. Patent Application No. _____, filed _____, which is directed to related technical subject matter. The identification of this U.S. Patent Application is not to be construed as a waiver of secrecy as to that application now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited application and the art cited therein during examination.

☐ 8. Copies of the documents were cited by or submitted to the Office in Application No. _____, filed _____, which is relied upon for an earlier filing date under

35 U.S.C. § 120. Thus, copies of these documents are not attached. 37 C.F.R. § 1.98(d).

It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449, and to indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 08-3038 referencing docket number 03166.0029.NPUS02.

Respectfully submitted,

Michael J. Bell (Reg.No. 39,604)
Michael J. Stimson (Reg. No. 45,429)

Date: April 18, 2003

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LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

PTO FORM 1449

ATTY. DOCKET NO.	APPLICATION NO.
03166.0029.NPUS02	09/994,927
APPLICANT: Hamilton *et al.*	
FILING DATE: November 28, 2001	GROUP: 1626

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	1.	2,593,563	04/1952	Huffman.			
	2.	3,876,797	04/1975	Biel *et al.*			
	3.	4,028,093	06/1977	Teach			
	4.	4,282,369	08/1981	Schirmer			
	5.	5,023,077	06/1991	Gevas			
	6.	5,057,610	10/1991	Pastor			
	7.	5,059,614	10/1991	Lepage			
	8.	5,273,989	12/1993	Schwab			
	9.	5,449,661	09/1995	Nakamura			
	10.	5,622,970	04/1997	Armistead			
	11.	5,624,894	04/1997	Boder			
	12.	5,728,659	03/1998	Naka			
	13.	5,741,819	04/1998	Illig *et al.*			
	14.	5,780,484	07/1998	Zelle			
	15.	5,811,434	09/1998	Zelle			
	16.	5,840,305	11/1998	Bukrinsky			
	17.	5,843,906	12/1998	Chandrakumar			
	18.	5,972,924	10/1999	Keep			
	19.	6,030,991	02/2000	Chan			
	20.	6,054,452	04/2000	Hamilton *et al.*			
	21.	6,177,466	01/2001	Sakaki			
	22.	6,444,643	09/2002	Steiner			

FOREIGN PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	23.	CH 459,172	09/1968	Switzerland			☐	☒

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

LIST OF REFERENCES CITED BY APPLICANT *(Use several sheets if necessary)* **PTO FORM 1449**	ATTY. DOCKET NO. 03166.0029.NPUS02	APPLICATION NO. 09/994,927
	APPLICANT Hamilton *et al.*	
	FILING DATE November 28, 2001	GROUP 1626

	24.	EP 0 633 145	01/1995	Europe			☒	☐
	25.	WO 98/37882	09/1998	PCT			☒	☐
	26.	WO 98/45259	10/1998	PCT			☒	☐
	27.	WO 99/00357	01/1999	PCT			☒	☐
	28.	WO 99/59959	11/1999	PCT			☒	☐

OTHER REFERENCES
(Including Author, Title, Date, Pertinent Pages, Etc.)

	29.	AGAFONOV, et al., Chemical Abstracts V. 109, #15 (1988)
	30.	Beilstein Registry Number 2164585
	31.	Beilstein Registry Number 2685041
	32.	Beilstein Registry Number 2769377
	33.	Beilstein Registry Number 2777922
	34.	Beilstein Registry Number 2798758
	35.	Beilstein Registry Number 469096
	36.	Beilstein Registry Number 7503934
	37.	BRAUN, W., Three-Dimensional Structure and Actions of Immunosuppressants and Their Immunophilins, *The FASEB Journal*, Vol. 9, January 1995
	38.	BURKHARD, P., et al., The Discovery of Steroids and Other Novel FKBP Inhibitors Using a Molecular Docking Program, *J. Mol. Biol.* (1999) 287, 853-858
	39.	CHAN, et al., Chemical Abstracts Vol. 126, 47207 (1996)
	40.	CHANDRAKUMAR, et al., Chemical Abstracts Vol. 130, 25348 (1998)
	41.	CHRISTNER, Claudia, et al., Synthesis and Cytotoxic Evaluation of Cycloheximide Derivatives as Potential Inhibitors of FKBP12 with Neuroregenerative Properties, *J. Med. Chem.*, 1999, 42, 3615-3622
	42.	COMANITA, et al., Chemical Abstracts V. 82, #21 (1975)
	43.	CONNOLLY, M.A., et al., GPI 1046 Elicits Neurite Outgrowth of Primary Sensory Neuronal Cultures, *Society of Neuroscience*, Abstract 677.13, Vol. 23, 1997
	44.	COSTANTINI, L.C., Neuroprotective and Regenerative Effects of Immunophilin Ligands in an Animal Model of Parkinson's Disease, *Society for Neuroscience*, Vol. 23, 1997
	45.	DESJARLAIS, et al., Chemical Abstracts Vol. 74, 53338 (1971)
	46.	DRAGOVICH, P.S., et al., Structure-Based Design of Novel, Urea-Containing FKBP12 Inhibitors, *Book of Abstracts*, 211th American Chemical Society National Meeting
	47.	EBERLING, J.L., et al., PET Evidence of Nigral Compensation in the MPTP Primate Model of

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		Parkinson's Disease, *Society of Neuroscience,* Abstract 677.14Vol. 23, 1997
	48.	FELIX, et al., Chemical Abstracts Vol. 93, 204202 (1980)
	49.	GALAT, Andrzej, Peptidylproline cis-trans-isomerases: Immunophilins, *Eur. J. Biochem.* 216, 689-707 (1993)
	50.	GERLACH, M., et al., MPTP Mechanisms of Neurotoxicity and their Implications for Parkinson's Disease, *European Journal of Pharmacology – Molecular Pharmacology Section,* 208 (1991) 273-286
	51.	GOLD, B.G., et al., A Nonimmunosuppressant FKBP-12 Ligand Increases Nerve Regeneration, *Experimental Neurology* 147, 269-278 (1997)
	52.	GOLD, B.G., et al., FKBP Ligands Speed Functional Recovery and Nerve Regeneration in the Rat Sciatic Nerve Following Oral Administration, *Society for Neuroscience,* Vol. 23, 1997
	53.	GOLD, Bruce G., FK506 and the Role of the Immunophilin FKBP-52 in Nerve Regeneration, *Drug Metabolism Reviews,* 31(3), 649-663 (1999)
	54.	GRABOWSKI, et al., Chemical Abstracts V. 127 #17 (1997)
	55.	GUO, H., et al., The Novel Small Molecule Immunophilin Ligand PI 1046 Stimulates Cholinergic Reinnervation of Deafferented Hippocampal Regions After Fimbria-Fornix Transection, *Society for Neuroscience,* Abstract 677.12, Vol. 23, 1997
	56.	HAMILTON, G.S., et al., FKBP12-Binding Domain Analogues of FK506 are Potent, Nonimmunosuppressive Neurotrophic Agents In Vitro and Promote Recovery in a Mouse Model of Parkinson's Disease, *Bioorganic & Medicinal Chemistry Letters,* Vol. 7, No. 13, pp. 1785-1790, 1997
	57.	HAMILTON, G.S., et al., Immunophilins: Beyond Immunosuppression, *Journal of Medicinal Chemistry,* Vol. 41, No. 26, December 17, 1998
	58.	HARRISON, R.K., et al., Substrate Specificities of the Peptidyl Prolyl Cis-Trans Isomerase Activities of Cyclophilin and FK-506 Binding Protein: Evidence for the Existence of a Family of Distinct Enzymes, *Biochemistry,* Vol. 29, No. 16, April 24, 1990
	59.	HICKS, T.P., et al., Alterations in the Form and Magnitude of Striatal Synaptic Plasticity in Slices from 6-OHDA-Lesioned Rats, *Society for Neuroscience,* Abstract 677.11, Vol. 23, 1997
	60.	HOLT, D.A., et al., Structure-Activity Studies of Synthetic FKBP Ligands as Peptidyl-Prolyl Isomerase Inhibitors, *Bioorganic & Medicinal Chemistry Letters,* Vol. 4, No. 2, pp. 315-320, 1994
	61.	IVERY, M. T. G., et al., Modeling the Interaction Between FK506 and FKBP12: a Mechanism for Formation of the Calcineurin Inhibitory Complex, *Bioorganic & Medicinal Chemistry,* Vol. 5, No. 2, pp. 217-232, 1997
	62.	JUSTICE, R.M., et al., The Detection of Proline Isomerase Activity in FK506-Binding Protein by Two-Dimensional ^{1}H NMR Exchange Spectroscopy, *Biochemical and Biophysical Research Communications,* Vol. 171, No. 1, 1990, pp. 445-450
	63.	KLIVENYI, P., et al., Neuroprotective Effects of Creatine in a Transgenic Animal Model of Amyotrophic Lateral Sclerosis, *Nature Medicine,* Vol. 5, No. 3, March 1999
	64.	KOFRON, J.L., et al., Determination of Kinetic Constands for Peptidyl Prolyl Cis-Trans Isomerases by an Improved Spectrophotometric Assay, *Biochemistry* 1991, 30, 6127-6134
	65.	KREMLEV, et al., Chemical Abstracts Vol. 77, 34101 (1972)

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	66.	LIANG, S., et al., Neuroimmunophilin Ligands Augment Serotonin Fiber Protection Following Lesions with Parachloroamphetamine (PCA), *Society for Neuroscience*, Abstract 677.10, Vol. 23, 1997
	67.	MCMAHON, S.B., et al., Peripheral Neuropathies and Neurotrophic Factors: Animal Models and Clinical Perspectives, *Neurobiology* 1995, 5:616-624
	68.	MUNROE, J.E., et al., Aryl Alkyl Ureas as Inhibitors of Influenza Virus, *American Chemical Society*, ed. 218, pt 1 (1999)
	69.	NAVIA, M.A., Rational Design of New Immunosuppressive Drugs, *Transplantation Proceedings*, 31, 1097-1098 (1999)
	70.	ROSS, D.T., et al., The Novel Neuroimmunophilin Ligand GPI 1046 Stimulates Morphological, Biochemical, and Behavioral Recovery in the Rat Intranigral 6-OHDA Parkinson's Disease Model, *Society for Neuroscience*, Abstract 677.7, Vol. 23, 1997
	71.	SAKAKI, et al., Chemical Abstracts Vol. 126, 212433 (1997)
	72.	SAUER, H., et al., Functional and Anatomical Consequences of Chronic Treatment with Non-Immunosuppressive Immunophilin Ligands after Striatal 6-Hydroxy-Dopamine Lesions in the Rat, *Society for Neuroscience*, Abstract 677.8, Vol. 23, 1997
	73.	SCHNEIDER, H., et al., Human Cyclophilin C: Primary Structure, Tissue Distribution, and Determination of Binding Specificity for Cyclosporins, *Biochemistry* 1994, 33, 8218-8224
	74.	SEXTON, Karen E., et al., Thiourea Inhibitors of 15-Lipoxygenase, *American Chemical Society*, ed. 218, pt. 1 (1999)
	75.	SHOULSON, Ira, Experimental Therapeutics of Neurodegenerative Disorders: Unmet Needs, *Science*, Vol. 282, November 6, 1998
	76.	SPITZFADEN, C., et al., Determination of the NMR Solution Structure of the Cyclophilin A-Cyclosporin A Complex, *Journal of Biomolecular NMR*, 4 (1994) 463-482
	77.	STEINER, J.P., et al., The Orally Active Neuroimmunophilin Ligand GPI 1046 Promotes Structural and Functional Recovery in the Mouse MPTP Model of Parkinson's Disease, *Society of Neuroscience*, Abstract 677.6, Vol. 23, 1997
	78.	STICHEL, Christine, et al., Experimental Strategies to Promote Axonal Regeneration After Traumatic Central Nervous System Injury, *Progress in Neurobiology*, Vol. 56, pp. 119-148, 1998
	79.	VALENTINE, H.L., et al., The Neuroimmunophilin Ligand of GPI 1046 stimulates Recovery Following Sciatic Nerve Injury, *Society for Neuroscience*, Abstract 677.9, Vol. 23, 1997
	80.	WANG, G.T., et al., Synthesis and FKBP Binding of Small Molecule Mimics of the Tricarbonyl Region of FK506, *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 9, pp. 1161-1166, 1994
	81.	WANG, M.S., et al., Comparative Dose-Dependence Study of FK506 and Cyclosporin A on the Rate of Axonal Regeneration in the Rat Sciatic Nerve, *The Journal of Pharmacology and Experimental Therapeutics*, Vol. 282, No. 2, 1997

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